Bilateral Pneumothoraces Hasten Mortality in AIDS Patients Receiving Secondary Prophylaxis with Aerosolized Pentamidine*

Association with a Lower Deco Prior to Receiving Aerosolized Pentamidine

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We have administered aerosolized pentamidine (AP) to 48 AIDS patients for secondary prophylaxis of Pneumocystis carinii pneumonia (PCP). Pentamidine 60 mg was administered by ultrasonic nebulization (Fisoneb) five times during the first two weeks and then every two weeks. The mean follow-up was 343 ± 22 days. PCP recurred in ten patients, 297 ± 33 days after starting AP therapy. All responded to anti-Pneumocystis therapy but two patients died of unrelated reasons (20 percent mortality). Five patients developed bilateral pneumothoraces 260 ± 35 days after starting AP therapy. Recurrence of PCP could be documented in only one patient. All died 66 ± 27 days after the onset of the first pneumothorax. Only 5 of 33 patients without recurrence of pneumonia or pneumothorax died during the study period (15 percent mortality). No association was found between the development of pneumothorax and age, smoking, previous respiratory or infectious problems, time from last PCP and the initiation of AP therapy, and treatment duration of last PCP. Patients with pneumothoraces had a significantly lower Deco (58.6 ± 2.6 percent predicted) prior to AP therapy than patients with recurrence of PCP without pneumothoraces (81.1 ± 2.1 percent predicted) or patients with no recurrence of PCP (67.2 ± 2.5 percent predicted) (p < 0.05, ANOVA). In conclusion, bilateral pneumothoraces are associated with a hastened mortality in patients receiving AP for secondary prophylaxis of PCP. Low Deco before AP therapy is associated with an increased risk of bilateral pneumothoraces in patients treated with AP for secondary prophylaxis of PCP.

Since the first description of the acquired immunodeficiency syndrome (AIDS) in 1981, it has become clear that pulmonary infection with Pneumocystis carinii is an important cause of morbidity and mortality. Pneumocystis carinii pneumonia (PCP) is the first serious opportunistic infection in more than 60 percent of patients with AIDS and about 80 percent of these patients develop PCP at least once. In association with a high recurrence rate of PCP, these statistics have led physicians to employ different prophylactic regimens to prevent a recurrence of PCP in AIDS patients.

Aerosolized pentamidine (AP) therapy has been shown to be effective in the prophylaxis of PCP. Among the complications of AP therapy, spontaneous pneumothorax with or without a recurrence of PCP has been reported. Although bullous pulmonary disease or spontaneous pneumothorax does occur in AIDS patients who are not receiving AP, it has been suggested that AIDS patients receiving AP are at increased risk for pneumothorax.

In this study, we present a group of AIDS patients who received AP for secondary prophylaxis of PCP. These patients had a high incidence of bilateral pneumothorax and this subgroup had an increased mortality. When compared with other AIDS patients receiving AP, those who developed pneumothoraces had a significantly decreased single breath carbon dioxide diffusion capacity (Deco) prior to receiving AP.

METHODS

Patients and Medication

Forty-eight consecutive consenting individuals older than 18 years of age and recovering from one or several episodes of confirmed PCP (by bronchoalveolar lavage) were studied. Inclusion criteria were a positive serologic test for human immunodeficiency virus infection and the ability of the patients to return to our outpatient clinic for follow-up visits and aerosol administration. None of the individuals received other prophylactic therapies for PCP. Treatment with azidothymidine (AZT) or 2-3-deoxyinosine was permitted as long as it was started at least 15 days before or after AP therapy. Patients suffering from poorly controlled obstructive lung disease were not given AP.

PCP = Pneumocystis carinii pneumonia; AZT = azidothymidine; AP = aerosolized pentamidine; Deco = single breath carbon monoxide diffusion capacity; MMAD = mass mean aerodynamic diameter

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Manuscript received September 10; revision accepted December 2.
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Bilateral Pneumothoraces Hasten Mortality in AIDS Patients (Renzi et al)

Table 1—Demographics and Survival of Patients*

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients, No.</th>
<th>Age, yr</th>
<th>AZT, No. (%)</th>
<th>Mean Follow-up, Days†</th>
<th>Death, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PCP, No PTX</td>
<td>33</td>
<td>36.9 ± 1.5</td>
<td>28 (85)</td>
<td>369 ± 29</td>
<td>5 (15)</td>
</tr>
<tr>
<td>PCP, No PTX</td>
<td>10</td>
<td>38.7 ± 2.8</td>
<td>9 (90)</td>
<td>297 ± 34</td>
<td>2 (20)</td>
</tr>
<tr>
<td>PTX</td>
<td>5</td>
<td>39 ± 2.4</td>
<td>5 (100)</td>
<td>260 ± 36</td>
<td>5 (100)†</td>
</tr>
</tbody>
</table>

*AZT = azidothymidine; PCP = Pneumocystis carinii pneumonia; PTX = pneumothorax.
†Until analysis or the appearance of a complication (PCP, PTX, or death).
‡P<0.05.
period. Two patients did not have any fever during their evaluation, had negative bronchoalveolar lavage for PCP, and had negative lung gallium scans. The diagnosis of PCP was confirmed in only one of five patients. *Pneumocystis carinii* was not found in the lung lavage of the other four patients. However, serum lactate dehydrogenase (LDH) was not measured in every patient at the time of hospital admission, direct monoclonal antibody staining for PCP was not performed on lung lavage, and transbronchial biopsies were not performed because of the risk of aggravating bronchopleural fistulas. Three patients received therapy for PCP (13 days in one patient and 21 days in the others with trimethoprim-sulfamethoxazole or pentamidine). Chest tubes were inserted in all patients on the side of their pneumothoraces and removed only when the air leaks ceased. The course was similar in the four patients with the longest survival. Pneumothoraces persisted on at least one side despite chest tube drainage. Two patients were treated with surgical pleurodesis on one side. All patients suffered from anorexia with progressive cachexia. Palliative measures were adopted with the consent of the patients. All patients died with at least one chest tube in place. Except for the patient who died 14 days after hospital admission, none of the deaths seemed related to PCP (dehydration, cachexia, bacterial pneumonia, septicemia).

Several factors may have influenced the appearance of pneumothorax in these patients. However, patients with pneumothorax did not seem to be more immunsuppressed since they did not have more prior episodes of PCP before starting AP therapy nor did they suffer from more infections during the study period (Table 3). Length of treatment of the last PCP, LDH value prior to AP therapy and the time between the onset of the last PCP and administration of AP were not significantly different in all three groups. The time elapsed between the beginning of AP therapy and the onset of complications was not different in patients with PCP or without pneumothorax. Patients with pneumothorax complained of symptoms for 6.8 ± 3.3 days prior to presentation to the hospital, whereas patients with PCP without pneumothorax were symptomatic for 18.6 ± 5 days prior to presenting to the hospital.

When pulmonary function tests prior to AP therapy were assessed, all spirometric values were normal except uncorrected and corrected Deco, which were low in all three groups (Table 4). Deco was significantly higher in the patients who went on to develop PCP without pneumothorax when compared with the other two groups. When the Deco of the patients with pneumothorax was compared with that of all other patients, uncorrected Deco was significantly lower (p = 0.024) and corrected Deco tended to be significantly lower (p = 0.053).

### DISCUSSION

*Pneumocystis carinii* is the most common cause of pneumonia in patients with AIDS. This pneumonia has an incidence of up to 80 percent in these patients.
and a high recurrence rate during the first year.\textsuperscript{4} Aerosolized pentamidine is effective for the primary and secondary prophylaxis of PCP in AIDS patients.\textsuperscript{4,5} As a prophylactic regimen, AP would be expected to increase the length of survival of patients with AIDS. However, this has yet to be shown, possibly because of the short length of follow-up in the published studies.\textsuperscript{4,5} We have presented the survival and respiratory complications of 48 patients receiving AP as secondary prophylaxis for PCP. During a study period of an average of 412 days, five patients developed pneumothoraces and all died a mean of 66 days after their first pneumothorax. These deaths represented 42 percent of all patient deaths and underline the importance of pneumothoraces as a negative effect on the survival of our AIDS patients. These results have an even more important impact since the occurrence of PCP without a pneumothorax did not affect survival.

The clinical course seemed the same in most of the five patients who developed pneumothoraces. Unre-solving air leaks were accompanied by anorexia and wasting until both patients and their physicians opted for conservative measures. Our results suggest that improvement in survival in these patients would thus be obtained by the prevention and not the treatment of their pneumothoraces.

Bullous lesions and pneumothoraces have been reported in the setting of acute PCP or as a late sequelae of PCP.\textsuperscript{9,15,19,22} Ivády et al\textsuperscript{21} described five radiologic stages of PCP in infants. In the third stage, the peripheral parts of the lung were described as "emphysematous." In the fifth stage, the authors described "emphysematous blebs" that can result in pneumothorax from rupture. In AIDS patients with PCP, cystic lesions have been reported on the chest roentgenogram in 7 and 10 percent of patients, respectively.\textsuperscript{14,15} When computed tomographic (CT) scans of the lungs were performed in 55 AIDS patients,\textsuperscript{3} bullous damage located predominantly in the apical and cortical areas of the lungs was found in 42 percent. However, only 70 percent of the patients with bullous lesions had suffered from one or more lung infection, which suggests that bullous disease of the lungs may not only be related to lung infection.

The incidence of pneumothorax in PCP seems to be increasing in frequency. Goodman et al\textsuperscript{12} reported seven cases of pneumothorax in 1986 when a review published in 1984\textsuperscript{23} had reported none.

When the occurrence of pneumothorax in AIDS patients was studied prospectively,\textsuperscript{22} the overall incidence was 2 percent with an increased relative risk in those having suffered from one or several PCPs and those receiving AP therapy. Several reports have also suggested that AIDS patients receiving AP may be at increased risk for pneumothorax.\textsuperscript{6,4} The exact incidence of pneumothorax in these patients is difficult to assess in view of the increased mortality and short length of follow-up in the published studies. However, the incidence varies between 0 percent\textsuperscript{24} and 6.3 percent.\textsuperscript{22} In our patients, the incidence of pneumothorax was 10.4 percent. The differences in incidence do not seem to be related to a technical factor since we used the same protocol for aerosolization as the Toronto Pentamidine Study Group.\textsuperscript{44} The increased incidence of pneumothorax also does not seem related to a problem of administration of pentamidine. Indeed, if a decrease in recurrence of PCP is a sign of proper administration of the medication, recurrence at one year in our study patients was comparable to that reported by Leoung et al\textsuperscript{2} (with the Respigard II). It thus seems that the AP was being deposited into the lungs and preventing recurrences of PCP. The high rate of pneumothoraces may be due to a longer follow-up in our patients or more underlying lung disease prior to AP therapy (decreased Dco).

Several factors could explain the occurrence of a relatively high incidence of pneumothorax in AIDS patients treated with AP. Aerosolized pentamidine is deposited in higher concentrations in the proximal airways and is less well-distributed to the periphery of the lungs.\textsuperscript{25} A slowly spreading, peripheral, necrotizing pneumonitis could extend to the pleural surface and cause a bronchopleural fistula with resultant pneumothorax as well as clinically apparent PCP as described in some studies.\textsuperscript{10,11,13} Another reason could be that patients with a history of PCP are at increased risk for a recurrence.\textsuperscript{4} Since PCP is associated with an increased risk of pneumothorax, recurrence of PCP in

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>FEV\textsubscript{1}, % Predicted</th>
<th>FVC, % Predicted</th>
<th>FEV/FVC, %</th>
<th>FEV 25-75%, % Predicted</th>
<th>Dco Uncorrected, % Predicted</th>
<th>Dco Corrected, % Predicted</th>
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<tbody>
<tr>
<td>No PCP, no PTX</td>
<td>33</td>
<td>98.1 ± 2.4</td>
<td>90.7 ± 2.4</td>
<td>83.1 ± 1.1</td>
<td>99.7 ± 5.1</td>
<td>61.3 ± 2.2</td>
<td>67 ± 2.1</td>
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<tr>
<td>PCP, No PTX</td>
<td>10</td>
<td>101 ± 6.4</td>
<td>91.7 ± 5.8</td>
<td>84.9 ± 1.2</td>
<td>105 ± 9.1</td>
<td>75.8 ± 3.3</td>
<td>81.1 ± 3.1</td>
</tr>
<tr>
<td>PTX</td>
<td>5</td>
<td>107 ± 1.9</td>
<td>100.4 ± 3.0</td>
<td>79.2 ± 1.8</td>
<td>92.8 ± 6.8</td>
<td>50.4 ± 1.3</td>
<td>58.6 ± 2.4</td>
</tr>
<tr>
<td>P value‡</td>
<td></td>
<td>0.46</td>
<td>0.39</td>
<td>0.19</td>
<td>0.72</td>
<td>0.001</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*FEV\textsubscript{1} = forced expiratory volume in the first second; FVC = forced vital capacity; FEV 25-75% = mean forced expiratory flow during the middle half of the FVC; Dco = carbon monoxide diffusing capacity; PCP = \textit{Pneumocystis carinii} pneumonia; PTX = pneumothorax.

†Corrected with Cotes formula.

‡ANOVA, comparison among all three groups.
our patients would thus be associated with an increased risk of pneumothorax.

It has also been suggested that AP may cause pneumothoraces through a direct or indirect effect. A direct toxic effect on cell growth and differentiation could explain lung necrosis and a bronchopleural fistula. However, the fact that the bullous lesions seem to appear at the periphery of the lungs, where less pentamidine is deposited, would argue against this possibility. The induction of cough by the sulfite in isethionate could lead to pneumothoraces in an abnormal lung with either decreased compliance due to parenchymal fibrosis or persistent cysts after PCP. None of our patients experienced pneumothoraces during AP therapy. Finally, increased survival in our patients may have increased the incidence of pneumothorax because of more recurrences of PCP, other lung infections, or the progression of bullous lung disease.

The reasons for pneumothoraces in our patients seem to be variable. A recurrence of PCP could certainly explain the pneumothorax in at least one of our patients. Two patients developed bilateral pneumothoraces without fever or an infiltrate on chest roentgenogram and with negative gallium lung scans, which would argue against a recurrence of PCP in these patients.

It is interesting that the only significant difference between the patients who developed pneumothorax and those who did not was an abnormal uncorrected single breath diffusion capacity prior to receiving AP. Part of this difference was explained by anemia, which is a possible sign of more severe disease in these patients. However, the Dco prior to AP therapy seemed lower in the patients who developed pneumothorax even after correction for the anemia ($p = 0.053$). We believe this difference to be significant in view of the small number of patients who developed pneumothorax. The small size of this group may also have masked significant differences in other baseline characteristics. The patients who presented with pneumothorax seemed to have an underlying lung disease that affected diffusion but not the lung volumes or the chest roentgenogram prior to receiving AP. Postinfectious pulmonary fibrosis could have been present in these lungs but it would be difficult to explain the normal chest roentgenograms in all the patients who had an important decrease in diffusion. Recurring PCP is a possibility since AP therapy was started relatively late after the last PCP (155 days) but the amount of AP administered is prophylactic and not therapeutic. It is thus difficult to explain the latency of 201 days between the administration of AP and pneumothorax and the same LDH levels in all groups.

"Emphysematous" cystic lung disease is a more likely possibility in view of the increased incidence of bullous lung disease described in AIDS patients, especially after PCP. Progression of these abnormal lung lesions either through the recurrence of PCP, another pulmonary infection, an immune mechanism, or a toxic effect of pentamidine could have led to the pneumothoraces presented. However, the Dco has been shown to increase in patients receiving AP for secondary prophylaxis of PCP. A toxic effect of AP would thus seem a less likely explanation.

In conclusion, our results show that pneumothorax is a significant complication in patients receiving AP for secondary prophylaxis of PCP and is associated with a high mortality. We do not know whether AP increases the incidence of pneumothorax. However, in AIDS patients requiring AP for secondary prophylaxis of PCP, a moderate to severe decrease in the single breath Dco identifies a group at increased risk of pneumothorax.

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